Please add the following new claims:

36. A method of treating an individual suffering from acute liver failure, comprising administration of a therapeutically effective amount of FLINT protein to said individual.

37. A method of treating an individual suffering from inflammation of the liver, comprising administration of a therapeutically effective amount of FLINT protein to said individual.

C10 38. A method of treating an individual suffering from abnormal hepatocyte apoptosis, comprising administration of a therapeutically effective amount of FLINT protein to said individual.

39. A method for treating an individual suffering from hepatitis, comprising administration of a therapeutically effective amount of FLINT protein to said individual.

Remarks

Applicants have amended the Specification and Claims. Applicants' amendments were made solely for the purpose of clarification and not for reasons of patentability.

Applicants request the deletion of Figures 2 and 4 from the specification as containing erroneous sequence information.

Applicants have amended claims 1-3 to insert the phrase "effective" in the context of therapeutic treatment using FLINT. Applicants assert no new matter has been added.

Applicants have added new claims 36-39.

Draftsman's Comments

The Draftsman issued a review objecting to the margins in some of the Figures. Applicants elect to withhold corrective action until after a determination of patentable subject matter has been made.

Sequence Rule Compliance

Applicants have amended the Specification according to the Examiner's request to identify Figure 1 with SEQ ID NO:1 and Figure 3 with SEQ ID NO:6 of the Sequence Listing.

35 U.S.C. § 112, Second Paragraph

Claims 1-3, and 6 stand rejected, allegedly "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants respectfully traverse.

The Examiner asserts, "As there is no art recognized definition of an mFLINT protein, nor is such a definition provided in the specification, the metes and bounds of the claim . . . cannot be determined." Applicants assert the term mFLINT is explicitly defined in the Specification and therefore the claim would be clear to the skilled artisan in the field of molecular biology. For example, at page 10, the term "mFLINT" is defined as "a mature FLINT, i.e. FLINT which does not have a leader . . . Examples of mFLINT include a protein having the amino acid sequence set forth in Figure 3 . . . ."

The second paragraph of Section 112 of the Patent Statute requires that patent claims must be sufficiently clear to allow one skilled in the art to understand what is claimed *Amgen v. Chugai*, 927 F.2d 1200, 1217 (Fed. Cir).

It would be clear to any artisan in the field of molecular biology that proteins may differ slightly in sequence and yet still possess the same activity. Hence, conservative amino acid changes often are silent in their effect on protein activity. While predicting with certainty which of the vast number of theoretical changes will be silent is impossible, neither is it wholly a black box. For example, most changes involving substitutions of a conservative nature

would remain silent, for example, a Leu to Ala. Applicants assert this would be *a priori* clear to the skilled artisan.

Applicants claim the use of FLINT or mFLINT to treat a variety of diseases thought to involve abnormal apoptosis mediated by the Fas-FasL pathway. Applicants have shown that FLINT inhibits the binding of Fas to FasL and thereby inhibits cellular apoptosis. The invention therefore relates to the use of FLINT or mFLINT proteins in such treatments, including FLINT variants of the sort referred to in the previous paragraph. Applicants have provided specific examples of FLINT gene and protein sequences in their Specification, as, for example, SEQ ID NO:1 and SEQ ID NO:6. While these specific sequences clearly describe *examples* of FLINT, they are not regarded as defining the *limits* of the claimed invention. As already noted, because of the redundancy of the genetic code, sequence variation can occur without a loss of essential function and this would be well recognized by the skilled artisan.

Applicants regard the invention as relating not only to the specific FLINT sequences disclosed, but also to sequences related structurally and functionally to the disclosed SEQ ID NO:1 and SEQ ID NO:6. A skilled artisan reading the claims and the Specification would recognize that the claims cover related sequences which, for example, make one or more conservative amino acid changes, or other changes that constitute closely related proteins having the ability to inhibit the binding of Fas to FasL. Indeed, the Examiner concedes this much on page 5 of the instant Office Action, "One of ordinary skill in the art would consider amino acid sequence variants of that depicted in Figure 4 to also be mFLINT proteins, and the definition provided by the specification encompasses these variants . . . ."

The Examiner further rejected Claims 1-3 and 6 under the second paragraph of Section 112 for reasons that are not

entirely clear to Applicants. The Examiner states, "the claims do not set forth what *particularly* the mFLINT is effective at doing" (emphasis in original). Elsewhere, "the claims do not establish a relationship between the administration of mFLINT and the treatment of any of the conditions. The claims encompass conditions wherein the mFLINT administration is not directly related to the disease and does not directly help treat the disease."

Applicants are unclear as to the issue under consideration by the Examiner. The effect of FLINT is clearly stated in each of the claims, and the specification, namely, a therapeutic effect in treating various human diseases. Claim 1, for example, is directed particularly at treating acute liver failure.

The Examiner further notes the claims do not "establish a relationship between the administration of mFLINT and the treatment of any of the conditions." Establishing such a relationship is not a requirement in the claims. To the degree that such a requirement exists, support therefor is most typically found in the Specification, not in the claims, as is true in the instant case.

The Examiner further states that the "claims encompass conditions wherein the mFLINT administration is not directly related to the disease and does not directly help treat the disease." Applicants respectfully challenge the basis for this assertion. Whether the administration of mFLINT *directly* treats a disease is not the issue. Applicants assert that mFLINT can be used to treat a variety of diseases that may be related to abnormal apoptosis mediated by the Fas-FasL pathway. The mechanism by which FLINT acts is not determinative as to the patentability of claimed invention, nor is it a requirement under the patent laws.

Applicants respectfully request withdrawal of this basis of the rejection and passage of the case to issue.

35 U.S.C. § 112, First Paragraph

Claims 1-3, and 6 were rejected under 35 U.S.C. section 112, first paragraph, allegedly as containing subject matter that was not enabled.

The test for non-enablement relates to whether the skilled artisan would need to resort to undue experimentation in order to practice the invention [*In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)]. In the instant case, the claims relate to the use of FLINT proteins for which Applicants intend not only the specific sequences disclosed, but also related sequences that are structurally and functionally closely related to the disclosed sequences. Case law is clear that some experimentation is permissible, and that the relevant issue relates to whether any needed experimentation is undue.

On the question of what is "undue experimentation," the Federal Circuit has elaborated the following factors as relevant to the issue: 1) quantity of experimentation necessary, 2) amount of direction or guidance presented, 3) presence or absence of working examples, 4) nature of the invention, 5) state of the prior art, 6) relative skill of those in the art, 7) the predictability of the art, 8) breadth of the claims. (*Id.*)

In the instant case, Applicants claims are directed at a genus of proteins designated as FLINT, or mFLINT, because it is *a priori* clear that substantial sequence variation can occur in most if not all proteins without there being a substantial alteration in the activity of the protein. Many changes in amino acid sequence are virtually silent, and therefore a fair claim scope must extend beyond that of a single sequence. The patent laws are intended to provide protection that is broad enough to encourage the patentee's disclosure, without which there would be no incentive to make such a disclosure.

While the theoretical number of FLINT variants is potentially enormous, the scope of the claims is directed at those variants that retain the biological activity and therapeutic utility of the parent molecule. It is likely that many changes of a conservative nature would not compromise the biological activity of FLINT. The principle that in general conservative changes can be made without altering activity is well accepted by the skilled artisan. This phenomenon rests on sound reasons relating to the chemical properties of amino acids associated with such changes. Generally, chemically similar amino acids are minimally disruptive of structure when substituting one for another from the same class. On the other hand, the impact of non-conservative changes is less certain. A skilled artisan would *a priori* suspect that non-conservative changes would be more likely to alter activity and therefore be less inclined to make and test such variants.

With the availability of modern cloning technologies and in vitro biological assays for testing anti-apoptotic activity of FLINT and FLINT variants, Applicants argue there would not be undue experimentation required to practice the invention. The experimentation necessary to produce FLINT variants and test them would be of a routine nature.

In view of the arguments put forth, Applicants have addressed all points of the rejection. Applicants respectfully request reconsideration of the claims and passage of this case to issue.

Respectfully submitted,

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